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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,072	10/14/2005	Ralf-Holger Voss	BB-140	1890

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SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO BOX 142950
GAINESVILLE, FL 32614-2950

EXAMINER	
KAUSHAL, SUMESH	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,072	VOSS ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 1008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *22-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *3/24/05* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 02/10/08 has been acknowledged and fully considered.

Election/Restrictions

Applicant's election without traverse of Group I claims 1-21 in the reply filed on 02/10/08 is acknowledged.

Claims 20-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 02/10/08.

Claim Objections

Claims 6-19 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim *cannot depend from any other multiple dependent claim* See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

Specification

The disclosure is objected to because of the following informalities:

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Specifically the application fails to comply with CFR 1.821(d), which states:
(d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing " in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application (see MPEP 2422.03).

For compliance with sequence rules, it is necessary to include the sequence in the "Sequence Listing" and identify them with SEQ ID NO. In general, any sequence that is disclosed and/or claimed as a sequence, i.e., as a string of particular bases or amino acids, and that otherwise meets the criteria of 37 CFR 1.821(a), must be set forth in the "Sequence Listing." (see MPEP 2422.03).

The instant specification fails to comply with the requirements for patent applications containing nucleotide sequence and/or amino acid sequence disclosures

because: *The specification fail to provide SEQ ID NO(s) for the nucleotide sequences disclosed. For example see, Figure-4.*

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 and 19-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The scope instant claims encompasses method for producing any hetrodimeric specific wild-type or chimeric TCR with any antigen specificity, wherein any and all domains (i.e. extracellular, transmembrane and intracellular domains) of the TCR-complex has been modified by random mutagenesis. At best the specification teaches a method for making the TCR complex wherein the alpha- and beta-chains of an MDM2(81-88)-specific TCR are used as alpha-chain and beta-chain, and wherein the Gly192 of the constant region of the alpha-chain and the Arg208 of the constant region of the beta-chain are exchanged by Arg 192 in the constant region of the alpha-chain and by Gly208 in the constant region of the beta-chain. Besides the MDM2(81-88)-specific TCR the specification as filed fails to disclose any other recombinant product

that would enable one skill art to practice the invention as claimed. The state of the art at the time of filing was such that the TCR is the most intricate membrane receptor structures known, wherein any mutation in the TCR-complex would cause unintentional conformational changes rendering the scope of invention as claimed highly unpredictable (see discussion below).

Applicant is referred to the guidelines for *Written Description Requirement* published January 5, 2001 in the Federal Register, Vol.66, No.4, pp.1099-1110. The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). In analyzing whether the written description requirement is met for the genus claim, it is first determined whether a representative number of species have been described by their complete structure. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. conserve motifs or domains).

In the instant case specification fails to disclose representative number of species by structure and function encompassed by the genus as claimed i.e. recombinant genetic material for the production of hetrodimeric specific wild-type or chimeric TCR with any antigen specificity, wherein any and all domains (i.e. extracellular, transmembrane and intracellular domains) of the TCR-complex has been modified by random mutagenesis. Furthermore the genus as claimed encompasses structurally and functionally distinct members other genus. Claiming all divergent species that achieve a result as contemplated by the application without defining the representative number of species by structure and function is not in compliance with the written description requirement. *Rather, it is an attempt to preempt the future before it has arrived.* "The written description requirement has several policy objectives. The essential goal' of the description of the invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed." In re Barker, 559 F.2d 588, 592 n.4, 194 USPQ 470, 473 n.4 (CCPA 1977). Another objective is to put the public in possession of what the applicant claims as the invention.

See Regents of the University of California v. Eli Lilly, 119 F.3d 1559, 1566, 43USPQ2d 1398, 1404 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089 (1998)."

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention as claimed is "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention (see Fed.Reg., Vo.66, No. 4, pp. 1099-11, January 5, 2001).

Since the specification fails to disclose a representative number of species defined by structure and function, it is not possible to envision the claimed composition. One cannot describe what one has not conceived. (See Fiddes v. Baird, 30 USP2d 1481 at 1483). Therefore, the lack of disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that the applicants were in possessions of the huge genera recited in the claims at the time the application was filed. Furthermore the possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v. WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).*

In the instant case the recombinant material required in the method as claimed has been defined only by a statement of function that broadly encompasses "any TCR-associated activity", which conveyed no distinguishing information about the identity of the claimed genetic material, such as its relevant structural or physical characteristics.

Therefore, a definition by function alone "does not suffice" to sufficiently describe a coding sequence "because it is only an indication of what the gene does, rather than what it is." *Eli Lilly*, 119 F.3 at 1568, 43 USPQ2d at 1406. See also *Fiers*, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing *Amgen Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991)). According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of even a single member of this genus would not be representative of other varaints and is insufficient to support the claim.

Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for method for producing a TCR complex wherein the alpha- and beta-chains of an MDM2(81-88)-specific TCR are used as alpha-chain and beta-chain, and wherein the Gly192 of the constant region of the alpha-chain and the Arg208 of the constant region of the beta-chain are exchanged by Arg 192 in the constant region of the alpha-chain and by Gly208 in the constant region of the beta-chain, does not reasonably provide enablement for method for producing any other hetrodimeric specific wild-type or chimeric TCR having any antigen specificity, wherein any and all domains (i.e. extracellular, transmembrane and intracellular domains) of the TCR-complex has been modified by mutagenesis to obtain the sterically arranged groups (as claimed) on TCR chains. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature Of Invention:

The instant invention relates to a method for producing hetrodimeric specific wild type or chimeric T-cell receptor (TCR).

Breadth Of Claims And Guidance Provided By The Inventor

The scope instant claims encompasses method for producing any hetrodimeric specific wild-type or chimeric TCR with any antigen specificity, wherein any and all domains (i.e. extracellular, transmembrane and intracellular domains) of the TCR-

complex has been modified by random mutagenesis. At best the specification teaches a method for making the TCR complex wherein the alpha- and beta-chains of an MDM2(81-88)-specific TCR are used as alpha-chain and beta-chain, and wherein the Gly192 of the constant region of the alpha-chain and the Arg208 of the constant region of the beta-chain are exchanged by Arg 192 in the constant region of the alpha-chain and by Gly208 in the constant region of the beta-chain. Besides the MDM2(81-88)-specific TCR the specification as filed fails to disclose any other recombinant product that would enable one skill art to practice the invention as claimed.

State Of Art And Predictability:

The state of the art at the time of filing was such that the TCR is the most intricate membrane receptor structures known in the art, wherein any mutation in the TCR-complex would cause unintentional conformational changes rendering the scope of invention as claimed highly unpredictable.

The TCR assembly is directed by unique polar contacts within the transmembrane domains, whereas extracellular contacts can contribute to stability and specificity. There is a segregation of functions among the subunits: the ligand-binding subunits have no intrinsic signalling capacity, signals are communicated instead via non-covalently associated, dimeric signalling modules that have cytoplasmic phosphorylation motifs. The functions of the domains within each subunit are topologically segregated: whereas the extracellular domains bind ligands and the cytoplasmic domains recruit signalling molecules, the sequences that direct assembly of signaling modules with their receptors reside primarily within the membrane-embedded and membrane-proximal segments. The specific mechanism of signal initiation has yet to be definitively determined for any of these receptor systems, and the concepts of the molecular architecture of activating immune receptor complexes have important consequences for how one envision signals to be propagated across the membrane.

Therefore understanding the structure and mechanics of activating immune receptors is crucial to the development of accurate models of any TCR functionality, especially in the context of the instant invention as claimed. The studies reviewed here represent a significant advance in the mapping of structurally and functionally relevant

molecular interactions within a group of receptor complexes that share a distinctive assembly mechanism and, consequently, a similar subunit arrangement. But what can these new and developing structural insights tell us about the mechanics of signal initiation through these important immune receptors as a group? As discussed in the cited art, the compartmentalization of sequence elements responsible for critical inter-subunit contacts is compatible with activation models involving major reorientations among extracellular and/or cytoplasmic domains. Therefore, only complete understanding of receptor triggering mechanisms would enable one skilled in the art to practice the invention as claimed. See Khuns et al IMMUNITY. 26:357-369, 2007, Khuns et al, IMMUNITY. 24(2):133-139, 2006. Call et al, NATURE REVIEWS IMMUNOLOGY 7:841-850,2007, Call et al MOL IMMUNOL. 40(18):1295-1305, 2004.

In addition, the scope of the instant invention encompasses genetic modification of a cell in-vivo, therefore the invention falls in the realm of gene therapy. The gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. One of the greatest challenges facing gene therapy is the efficient transfer and stable expression of transgene in appropriate tissues. The NIH expert panel found that all gene transfer vectors are ineffective and it is not understood how they interact with the host It has been difficult to predict the efficiency and out come of transduced therapeutic genes because various factors govern the expression and/or therapeutic potential of transduced genes in vivo. The transduction of target cells represents the first critical step in gene therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors. Furthermore, in-vitro gene transfer studies are not predictive of in-vivo gene therapy because gene transfer frequency is much higher in-vitro models where most of cells are under going rapid cell division, which is quite not the case in-vivo environment. In addition, besides the limitations in gene transfer the problem to selectively target cells in vivo is still one of the most difficult obstacles to overcome. For example, the vector particles binds to many cells they encounter in vivo and therefor would be diluted out t before reaching their targets. (see Raper, SURGERY, 137(5):487-492, 2005)

Since the specification fails to disclose a representative number of species defined by structure and function (supra), it is unclear how one skilled in the art would make and use the invention as claimed. The applicant's disclosure does not enable one skilled in the art to practice the invention as claimed without further undue amount of experimentation, which requires the identification and characterization of any and all TCR domains associated with any and all antigens followed evaluation of each TCR chain separately in order to introduce required conformational changes. At issue, under the enablement requirement of 35 U.S.C. 1 12, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the circumstances. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970).

In instant case producing wild-type or chimeric TCR receptors specific to any antigen, wherein in first and second chain is mutated to provide sterically arranged sites (as claimed) is not considered routine in the art and without sufficient guidance to a specific TCR structure associated with corresponding mutated sites designated on each TCR chain, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and limited amount of guidance provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are generally narrative and indefinite, failing to conform with current U.S. practice. They appear to be a literal translation into English from a foreign document and are replete with grammatical and idiomatic errors.

Claim 1 recites "Method for producing", changing the current limitation to "A method for producing" has been suggested. In addition the dependent claims recite limitation "Method according to". Changing current limitation to "The method according to" has been suggested over come current rejection.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sumesh Kaushal/
Primary Examiner, Art Unit 1633

Sumesh Kaushal
Primary Examiner
Art Unit 1633